

REMARKS

Amendment to the claims

Claims 97 and 166 are each amended herein to indicate that individual microchips in an array or individual arrays in an array are physically separated from each other as disclosed in the specification in the description of Figure 2A, and at page 40, beginning at line 21 which states,

The arrays may be separated physically from each other or by hydrophobic surfaces. One possible way to utilize the hydrophobic strip separation is to use technology such as the Iso-Grid Microbiology System produced by QA Laboratories, Toronto, Canada..

Claims 160 and 170 are amended to correct grammatical errors.

The amendments therefore include no new matter.

Election/Restriction

The examiner asserted that because the applicant previously elected the subject matter of Group III and that new claim 176 is assertedly drawn to a method similar to the subject matter of non-elected Group I, claim 176 is withdrawn from consideration as being directed to a non-elected invention.

The applicant respectfully traverses. The subject matter of claim 176 is specifically directed to use of a support recited in prior claims. Thus, a search of the subject matter recited the "support" product claims under consideration would necessarily allow the examiner to identify any relevant prior art with respect to the "use" subject matter of claim 176. Since the subject matter of all claims can be searched in a single search, the applicant submits that examination of all claims does not constitute an undue burden on the examiner and requests that claim 176 be examined with all other claims under consideration.

In the alternative, the applicant requests that, upon a finding of allowable subject matter recited in claims from which claim 176 depends, claim 176 be rejoined and allowed to issue with the other allowable claims.

Objections to the specification

The examiner objected to the specification asserting that the title is not descriptive. Amendment to the title obviates this rejection.

Claims 160 and 170 were objected to for including incorrect syntax. Amendment to these claims overcome the objections.

The rejection under 35 USC §112, first paragraph

Claims 97 and 157-165 were rejected under 35 USC §112, first paragraph, for allegedly lacking written descriptive support in the specification. The examiner asserted that the specification as originally filed does not teach or describe the claimed "microchips" as recited in claim 97 and that the term constitutes new matter.

The applicant respectfully disagrees. The present application explicitly discloses "microchip" as claimed throughout the specification.

For example, at page 17, beginning at line 8, the specification discloses:

In one exemplary embodiment, both sets of oligonucleotide probes would be probes of six bases in length, i.e., 6-mers. In this instance, each set of oligos contain 4096 distinct probes. The first set [of, *sic*] probes is preferably fixed in an array on a microchip, most conveniently arranged in 64 rows and 64 columns. The second set of 4096 oligos would be labeled with a detectable label and dispensed into a set of distinct tubes. In this example, 4096 of the chips would be combined in a large array, or several arrays. After hybridizing the nucleic acid fragments, a small amount of the labeled oligonucleotides would be added to each microchip for the second hybridization step, only one of each of the 4096 nucleotides would be added to each microchip.

At page 23, beginning at line 22, the specification also discloses:

One set of such probes of length F (4^F) would be fixed in a square array on a microchip--which may be in the range of 1 mm^2 or 1 cm^2 . In the present example, these would be arranged in 64 rows and 64 columns. Naturally, one would ensure that the oligo probes were attached, or otherwise immobilized, to the microchip surface so that were able to take part in hybridization reactions. Another set of oligos of length P, 4^P in number, would be also synthesized. The oligos in this "P set" would be labeled with a detectable label and would be dispensed into a set of tubes (FIG. 2A, FIG. 2B and FIG. 2C).

At page, 24, beginning at line 28, the specification further discloses:

At this stage, each microchip would contain certain hybridized complexes.

At p. 25, beginning at line 7, the specification provides:

After washing to remove the non-complementary nucleic acid fragments that did not hybridize, a small amount of the labeled oligonucleotides in set P would be added to each microchip for hybridization to the nucleic acid fragment tails of unknown sequence that protrude from the probe:fragment complexes. Only one of each of the 4^P nucleotides would be added to each microchip.

At p. 25, beginning at line 23, the specification further provides:

At this stage, each microchip would then contain certain 'secondary hybridized complexes.

Accordingly, the term microchip is taught to be an embodiment contemplated by the invention and properly claimed. The applicant therefore submits that the "new matter" rejection may be withdrawn.

The rejection under 35 USC §102(b)

Claims 97, 159-160, 163-166, 169-170 and 173-175 were rejected under 35 USC §102(b) for being directed to subject matter assertedly anticipated by the disclosure of Southern, Genomics (1992) 13:1008 [hereinafter "Southern"]. The examiner relies basically on Figure 3 in Southern to support the rejection.

The legend for Figure 3 states, "The plate carries four copies of an array of all 256 octapurines, one in each of the four quadrants." With this arrangement Southern is able to carry out four identical hybridization reactions at the same time. Southern does not, however, teach or suggest that the four copies of the arrays are or can be physically separated as recited in the instant claims, and thus be used to carry out four different hybridization reactions at the same time as provided with the present invention. See, for example, p. 42 in the present application, beginning at line 7, which states,

Two basic problems have to be solved. Manipulation with small (2-3 mm) chips, and parallel execution of thousands of the reactions. The solution of the invention is to keep the chips and the probes in the corresponding arrays. In one example, chips containing 250,000 9-mers are synthesized on a silicon wafer in the form of 8x8 mm plates (15 µM/oligonucleotide, Pease et al., 1994) arrayed in 8x12 format (96 chips) with a 1 mm groove in between. Probes are added either by multichannel pipet or pin array, one probe on one chip. To score all 4000 6-mers, 42 chip arrays have to be used, either using different ones, or by reusing one set of chip arrays several times.

The present invention thus overcome technical problems associated with arrays known in the art and is therefore distinct from these prior art products. Accordingly, the applicant submits the rejection over Southern may properly be withdrawn.

The rejection under 35 USC §102(e)

Claims 97, 157-160, 163-170 and 173-175 were also rejected under 35 USC §102(e) for being directed to subject matter assertedly anticipated by the disclosure of Winkler, US Patent No. 5677195 [hereinafter "Winkler"]. Specifically, the examiner relies on Figure 12 and the following disclosures in Winkler.

Col. 7, lines 10-41:

8. Predefined Region: A predefined region is a localized area on a substrate which is, was, or is intended to be used for formation of a selected polymer and is otherwise referred to herein in the alternative as "reaction" region, a "selected" region, or simply a "region." The predefined region may have any convenient shape, e.g., circular, rectangular, elliptical, wedge-shaped, etc. In some embodiments, a predefined region and, therefore, the area upon which each distinct polymer sequence is synthesized is smaller than about 1 cm^2 , more preferably less than 1 mm^2 , and still more preferably less than 0.5 mm^2 . In most preferred embodiments the regions have an area less than about $10,000\text{ }\mu\text{m}^2$ or, more preferably, less than $100\text{ }\mu\text{m}^2$. Within these regions, the polymer synthesized therein is preferably synthesized in a substantially pure form.

9. Substantially Pure: A polymer is considered to be "substantially pure" within a predefined region of a substrate when it exhibits characteristics that distinguish it from other predefined regions. Typically, purity will be measured in terms of biological activity or function as a result of uniform sequence. Such characteristics will typically be measured by way of binding with a selected ligand or receptor. Preferably the region is sufficiently pure such that the predominant species in the predefined region is the desired sequence. According to preferred aspects of the invention, the polymer is at least 5% pure, more preferably more than 10% to 20% pure, more preferably more than 80% to 90% pure, and most preferably more than 95% pure, where purity for this purpose refers to the ratio of the number of ligand molecules formed in a predefined region having a desired sequence to the total number of molecules formed in the predefined region.

Col. 16, lines 22-53:

In another embodiment, the invention provides a multichannel solid-phase synthesizer as shown in FIG. 12. In this embodiment, a collection of delivery lines such as a manifold or collection of tubes 1000 delivers activated reagents to a synthesis support matrix 1002. The collection of tubes 1000 may take the

form of a rigid synthesis block manifold which can be precisely aligned with the synthesis support matrix 1002. The support matrix contains a plurality of reaction regions 1004 in which compounds may be immobilized or synthesized. In preferred embodiments, the reaction regions include synthesis frits, pads, resins, or the like.

The solutions delivered to the individual reactant regions of the support matrix flow through the reaction regions to waste disposal regions, recycling tank(s), separators, etc. In some embodiments, the reaction solutions simply pass through the reaction regions under the influence of gravity, while in other embodiments, the solutions are pulled or pushed through the reaction regions by vacuum or pressure.

The individual reaction regions 1004 of the support matrix are separated from one another by walls or gaskets 1006. These prevent the reactant solution in one reaction region from moving to and contaminating adjacent reaction regions. In one embodiment, the reaction regions are defined by tubes which may be filled with resin or reaction mixture. The gasketing allows close contact between the support matrix 1002 and a "mask" (not shown). The mask serves to control delivery of a first group reactant solutions through predetermined lines (tubes) to a first set of reaction regions. By ensuring close contact between the delivery tubes 1000, the mask, and the support matrix 1002, the probability that reaction solutions will be accidentally [*sic*] added to the wrong reaction site is reduced.

Looking at the description of Fig. 12, a support matrix [1002] is provided having individual reaction regions [1004]. Collection tubes [1000] deliver reaction solutions to reaction regions on the support matrix in order to allow for synthesis of a specific polymer at each individual reaction region. In the end, the individual reaction regions have a substantially pure polymer species located thereon, the final product in its entirety thus being a single array of one or more polymers on the support matrix.

The single array taught by Winkler is distinct from an array of microchips or an array of arrays as recited in the rejected claims. The present specification makes it clear that the claimed microchip is an array of arrays. For example, at page 17, beginning at line 8, the specification discloses:

In one exemplary embodiment, both sets of oligonucleotide probes would be probes of six bases in length, i.e., 6-mers. In this instance, each set of oligos contain 4096 distinct probes. The first set [of, *sic*] probes is preferably fixed in an array on a microchip, most conveniently arranged in 64 rows and 64 columns. The second set of 4096 oligos would be labeled with a detectable label and dispensed into a set of distinct tubes. In this example, 4096 of the chips would be combined in a large array, or several arrays.

Thus 4096 oligos having distinct sequences are arrayed on a chip, 4096 such chips are produced, and these 4096 chips are then arrayed.

Winkler neither teaches nor suggests such a product; i.e., each region in the Winkler array (if it assumed that each region is an array in itself) has identical polymers in the region, and as such, the rejection may properly be withdrawn.

The rejections under 35 USC §103

The examiner rejected claims 162 and 172 under 35 USC §103 for being directed to subject matter allegedly rendered obvious by the disclosure of Winkler in view of the disclosure of Augenlicht, US Patent No. 4981783 [hereinafter "Augenlicht"]. For reasons discussed above, the disclosure of the primary reference Winkler cannot anticipate the subject matter of the broad claims because it fails to disclose each and every limitation of these claims. Because the limitations of the broad claims attach to the subject matter of the dependent claims, Winkler cannot disclose all limitations of these claims either. Adding in the disclosure of Augenlicht fails to correct this deficiency in the Winkler disclosure because Augenlicht does not disclose arrays of physically separate microchips or arrays wherein the microchip or array had oligonucleotides with different sequences attached. Absent a combination of references that teach all limitations of the claims, the combined disclosures cannot anticipate the subject matter of the claims (see MPEP §706.02(j)), and the rejection over the disclosures of Winkler and Augenlicht may properly be withdrawn.

The same is true for the rejection of claims 161 and 171 over the combined disclosures of Winkler and Stratagene 1988 [hereinafter "Stratagene"]. The failure of Winkler to disclose or suggest all limitations of the claims is not corrected by combining it with the disclosure of Stratagene which, like Augenlicht above, does not teach or suggest arrays of physically separate microchips or arrays wherein the microchip or array had oligonucleotides with different sequences attached. Accordingly, this rejection may also properly be withdrawn.

The double patenting rejection

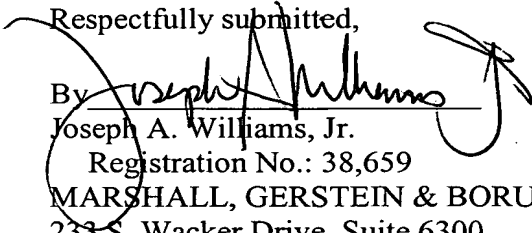
The applicant acknowledges the double patenting rejection and will address this rejection once otherwise allowable subject matter has been found in the instant application.

CONCLUSION

In view of the amendments and remarks made herein, the applicant submits that all claims are in condition for allowance and requests notification of the same.

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